

1 Claims

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4 1. A method of killing cancer cells, comprising
5 administration to said cells of an effective
6 amount of a c-FLIP inhibitor, wherein the c-
7 FLIP inhibitor is administered as the sole
8 cytotoxic agent in the substantial absence of
9 other cytotoxic agents.

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11 2. A method of treating cancer comprising
12 administration to a subject in need thereof a
13 therapeutically effective amount of a c-FLIP
14 inhibitor, wherein the c-FLIP inhibitor is
15 administered as the sole cytotoxic agent in
16 the substantial absence of other cytotoxic
17 agents.

18

19 3. A method of killing cancer cells having a p53
20 mutation, comprising administration to said
21 cells of:
22 (a) a c-FLIP inhibitor and
23 (b) a chemotherapeutic agent, wherein the
24 chemotherapeutic agent is a thymidylate
25 synthase inhibitor, a platinum cytotoxic agent
26 or a topoisomerase inhibitor.

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28 4. A method of treating cancer associated with a
29 p53 mutation comprising administration to a
30 subject in need thereof
31 (a) a c-FLIP inhibitor and
32 (b) a chemotherapeutic agent, wherein the

- 1 chemotherapeutic agent is a thymidylate
2 synthase inhibitor, a platinum cytotoxic agent
3 or a topoisomerase inhibitor.
- 4
- 5 5. The method according to claim 3 or claim 4,
6 further comprising administration of:
7 (c) a death receptor binding member.
- 8
- 9 6. The method according to claim 5, wherein the
10 death receptor is FAS.
- 11
- 12 7. The method according to claim 6, wherein the
13 binding member is the FAS antibody CH11.
- 14
- 15 8. The method according to any one of claims 3 to
16 7, wherein the chemotherapeutic agent is 5-FU,
17 oxaliplatin or CPT-11.
- 18
- 19 9. The method according to claim 8, wherein the
20 chemotherapeutic agent is 5-FU or oxaliplatin.
- 21
- 22 10. The method according to any one of claims 3 to
23 9, wherein the c-FLIP inhibitor and
24 the chemotherapeutic agent are administered in
25 a potentiating ratio.
- 26
- 27 11. The method according to claim 10, wherein the
28 c-FLIP inhibitor and
29 the chemotherapeutic agent are administered in
30 concentrations sufficient to produce a CI of
31 less than 0.85.
- 32

- 1 12. The method according to any one of claims 3 to
2 11, wherein the p53 mutation is such that p53
3 is completely inactivated in the cancer cells.
4
5 13. The method according to any one of claims 3 to
6 11, wherein the p53 mutation is a missense
7 mutation resulting in the substitution of
8 histidine (R175H mutation) or a missense
9 mutation resulting in the substitution of
10 tryptophan (R248W mutation) for arginine.
11
12 14. The method according to any one of claims 1 to
13 13, wherein said c-FLIP inhibitor is an RNAi
14 agent, which modulates expression of a c-FLIP
15 gene.
16
17 15. The method according to claim 14 wherein the
18 c-FLIP inhibitor is an RNAi agent having
19 nucleotide sequence
20 AAG CAG TCT GTT CAA GGA GCA (SEQ ID NO: 1) or
21 AAG GAA CAG CTT GGC GCT CAA (SEQ ID NO: 2)
22
23 16. The use of a c-FLIP inhibitor as the sole
24 cytotoxic agent in the preparation of a
25 medicament for treating cancer, wherein the
26 medicament is for treatment in the substantial
27 absence of other cytotoxic agents.
28
29 17. The use of
30 (a) a c-FLIP inhibitor and
31 (b) a chemotherapeutic agent, wherein the
32 chemotherapeutic agent is a thymidylate

1 synthase inhibitor, a platinum cytotoxic agent
2 or a topoisomerase I inhibitor
3 in the preparation of a medicament for
4 treating cancer associated with a p53
5 mutation.

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7 18. The use according to claim 17, wherein the
8 medicament further comprises:
9 (c) a death receptor binding member.

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11 19. The use according to claim 18, wherein the
12 death receptor is FAS.

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14 20. The use according to claim 19, wherein the
15 binding member is the FAS antibody CH11.

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17 21. The use according to any one of claims 17 to
18 20, wherein the chemotherapeutic agent is 5-
19 FU, oxaliplatin or CPT-11.

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21 22. The use according to claim 21, wherein the
22 chemotherapeutic agent is 5-FU or oxaliplatin.

23

24 23. The use according to any one of claims 17 to
25 21, wherein the c-FLIP inhibitor and
26 the chemotherapeutic agent are present in a
27 potentiating ratio.

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29 24. The use according to claim 23, wherein the c-
30 FLIP inhibitor and the chemotherapeutic agent
31 are present in concentrations sufficient to

- 1 produce a CI of less than 0.85.
- 2
- 3 25. The use according to any one of claims 17 to
4 24, wherein the p53 mutation is such that p53
5 is completely inactivated in the cancer cells.
- 6
- 7 26. The use according to any one of claims 17 to
8 24, wherein the p53 mutation is a missense
9 mutation resulting in the substitution of
10 histidine (R175H mutation) or a missense
11 mutation resulting in the substitution of
12 tryptophan (R248W mutation) for arginine.
- 13
- 14 27. The use according to any one of claims 16 to
15 26, wherein said c-FLIP inhibitor is an RNAi
16 agent, which modulates expression of a c-FLIP
17 gene.
- 18
- 19 28. The use according to claim 27 wherein the c-
20 FLIP inhibitor is an RNAi agent having
21 nucleotide sequence
22 AAG CAG TCT GTT CAA GGA GCA (SEQ ID NO: 1) or
23 AAG GAA CAG CTT GGC GCT CAA (SEQ ID NO: 2).
- 24
- 25
- 26 29. A pharmaceutical composition for the treatment
27 of cancer, wherein the composition comprises a
28 c-FLIP inhibitor as the sole cytotoxic agent
29 and a pharmaceutically acceptable excipient,
30 diluent or carrier, wherein the composition is
31 for treatment in the absence of other
32 cytotoxic agents.

- 1
- 2 30. A pharmaceutical composition for the treatment
- 3 of a cancer associated with a p53 mutation,
- 4 wherein the composition comprises (a) a c-FLIP
- 5 inhibitor
- 6 (b) a chemotherapeutic agent, wherein the
- 7 chemotherapeutic agent is a thymidylate
- 8 synthase inhibitor, a platinum cytotoxic agent
- 9 or a topoisomerase I inhibitor
- 10 and
- 11 (c) a pharmaceutically acceptable excipient,
- 12 diluent or carrier.
- 13
- 14
- 15 31. The composition according to claim 30, further
- 16 comprising (c) a death receptor binding
- 17 member.
- 18
- 19 32. The composition according to claim 31, wherein
- 20 the death receptor is FAS.
- 21
- 22 33. The composition according to claim 32, wherein
- 23 the binding member is the FAS antibody CH11.
- 24
- 25 34. The composition according to any one of claims
- 26 30 to 33, wherein the chemotherapeutic agent
- 27 is 5-FU, oxaliplatin or CPT-11.
- 28
- 29 35. The composition according to claim 34, wherein
- 30 the chemotherapeutic agent is 5-FU or
- 31 oxaliplatin.
- 32

- 1 36. The composition according to any one of claims
2 30 to 36, wherein the c-FLIP inhibitor and
3 the chemotherapeutic agent are present in a
4 potentiating ratio.
- 5
- 6 37. The composition according to claim 36, wherein
7 the c-FLIP inhibitor and
8 the chemotherapeutic agent are present in
9 concentrations sufficient to produce a CI of
10 less than 0.85.
- 11
- 12 38. The composition according to any one of claims
13 30 to 37, wherein the p53 mutation is such
14 that p53 is completely inactivated in the
15 cancer cells.
- 16
- 17 39. The composition according to any one of claims
18 30 to 37, wherein the p53 mutation is a
19 missense mutation resulting in the
20 substitution of histidine (R175H mutation) or
21 a missense mutation resulting in the
22 substitution of tryptophan (R248W mutation)
23 for arginine.
- 24
- 25 40. The composition according to any one of claims
26 29 to 39, wherein said c-FLIP inhibitor is an
27 RNAi agent, which modulates expression of a c-
28 FLIP gene.
- 29
- 30 41. The composition according to claim 40 wherein
31 the c-FLIP inhibitor is an RNAi agent having
32 nucleotide sequence

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1 AAG CAG TCT GTT CAA GGA GCA (SEQ ID NO: 1) or
2 AAG GAA CAG CTT GGC GCT CAA (SEQ ID NO: 2).

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4 42. A kit for the treatment of cancer associated
5 with a p53 mutation, said kit comprising
6 (a) a c-FLIP inhibitor and
7 (b) a chemotherapeutic agent, wherein the
8 chemotherapeutic agent is a thymidylate
9 synthase inhibitor, a platinum cytotoxic agent
10 or a topoisomerase I inhibitor and
11 (c) instructions for the administration of (a)
12 and (b) separately, sequentially or
13 simultaneously.

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17 43. An RNAi agent having nucleotide sequence
18 AAG CAG TCT GTT CAA GGA GCA (SEQ ID NO: 1) or
19 AAG GAA CAG CTT GGC GCT CAA (SEQ ID NO: 2).

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21

22 44. An RNAi agent consisting of nucleotide
23 sequence
24 AAG CAG TCT GTT CAA GGA GCA (SEQ ID NO: 1) or
25 AAG GAA CAG CTT GGC GCT CAA (SEQ ID NO: 2).

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